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ATTEMPTS TO PREPARE 1-METHYL 2-METHOXYPIPERIDINE; THE HYDROGENATION OF CERTAIN PYRIDINE DERIVATIVES.

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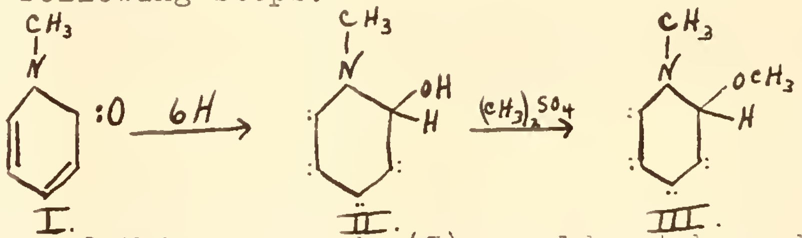
INTRODUCTION.

This research was started with a view to synthesizing 1-methyl 2-methoxypiperidine and some of its homologs, in order to study their physiological action, but this has not yet been accomplished. However, certain 2-substituted pyridines have been prepared and their transformation into the corresponding piperidines attempted; this paper deals with the results of these trials.

Four pyridine derivatives were used, successively, as starting points for the synthesis: 1-methyl 2-pyridone, 2-aminopyridine, 2-chlorpyridine, and 2-methoxypyridine.

1. The most direct method appeared to be from 1-methyl 2-pyridone by the following steps:-



But the reduction of this compound (I), could not be made to yield 1-methyl 2-piperidol (II). Von Pechmann and Baltzer[1] found that the action of sodium amalgam on 1-ethyl 2-pyridone destroys the ring, giving ethyl amine, so less energetic agents,

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1. Ber. 24 (1891), 3144.

known to be capable of reducing CO to CHOH, were tried at first.

a. "Aluminium amalgam" in dilute sulphuric acid.[2]

b. Electro-reduction in 10% sulphuric acid, with mercury cathode and lead anode.[3]

c. Sodium ethoxide and zinc dust in absolute alcohol.[4]

In spite of the prolonged action of excessive amounts of these reagents, no reduction whatever took place; in each case, the 1-methyl 2-pyridone was recovered unchanged.

d. Hydrogen at three atmospheres' pressure, in the presence of platinum black suspended in dilute hydrochloric acid. The catalyst was obtained by shaking platinum oxide with hydrogen in the presence of pyridine in hydrochloric acid solution. The oxide was prepared by the method of Adams and Voorhees[5]. This method gave partial reduction, but only four atoms of hydrogen per molecule were absorbed, with the formation of 1-methyl 2-piperidone.

2. The next starting point was 2-aminopyridine, the proposed

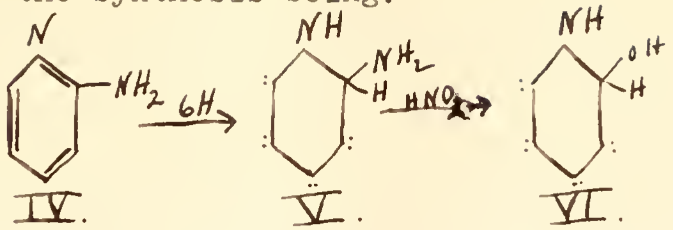
2. D. R. P. 157,300.

3. Tafel, Ber. 37 (1904), 3189

4. Chichibabin, Ber. 37 (1904), 1371.

5. J. Amer. Chem. Soc., 44 (1922), 1397.

steps in the synthesis being:-



followed by methylation.

The formation of 2-aminopiperidine has been reported,[6] but no proof of the structure is given and the compound is not recognized in the literature. Marckwald[7] reduced 2-aminopyridine with sodium and alcohol, and obtained, besides ammonia and piperidine, a higher-boiling base in such small quantity that it could not be analyzed. The results of the present investigation show that 2-aminopiperidine cannot be formed in an alkaline reduction medium, and that the possibility of its existence is doubtful. The hydrogenation was carried out with three different forms of platinum as catalyst.

a. Colloidal platinum, prepared by the method of Skita[8], in aqueous solution containing an excess of hydrochloric acid, to prevent the splitting-off of ammonia[9].

b. Platinum black, using excess hydrochloric acid, both in aqueous and in alcoholic solution.

c. Freshly prepared platinum oxide in neutral aqueous solution.

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6. A. M. Levy, Inaug.-Diss., Erlangen, On the Reduction of Alkylene Cyanides.
7. Ber. 27 (1894), 1330.
8. Ber. 45 (1912), 3589.
9. Ber. 52 (1919), 1520.

Methods a & b gave quantitative yields of tetrahydro-aminopyridine; no amount of shaking with hydrogen at 3-2/3 atmospheres could induce the molecule of aminopyridine to take up more than four atoms. Method c gave more complete hydrogenation; it actually permitted the absorption of eight atoms per molecule, with formation of ammonia and piperidine. This indicated that there is a possibility of obtaining aminopiperidine, provided the reaction is stopped at the right point. The introduction of two atoms of hydrogen into the molecule of tetrahydroaminopyridine was therefore attempted, but the result was four atoms for half the tetrahydro-aminopyridine used, the remainder being unchanged. Only ammonia, piperidine, and tetrahydro-aminopyridine could be isolated from the reduction product.

Tetrahydro-aminopyridine in the free state was found to be unstable; it is hydrolyzed by boiling water, and by cold concentrated potassium hydroxide, to ammonia and 2-piperidone. An aqueous solution of the free base, prepared by decomposing the hydrochloride with silver oxide, has a strong ammoniacal odor, with scarcely any resemblance to that of piperidine, but this odor is not due to free ammonia, because nitrogen, bubbled through the solution at room temperature for twelve hours, carries no ammonia with it. In dilute sulphuric acid, the base was totally indifferent to nitrous acid, both at 0°, and at 100°, yet in the free state, it gave the Rimini test[10] for the primary amino- group. A detailed study of the compound offered interesting

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[10] Mulliken, Identification of Pure Organic Compounds, Test 2.25.

possibilities, but as it appeared to be useless as an intermediate in the synthesis of methoxypiperidine, it was not further investigated.

3. The regulated hydrogenation of 2-chlorpyridine was next attempted. This compound has been reduced to piperidine and hydrochloric acid with sodium and alcohol by O. Fischer[11], but it was thought possible that a high concentration of hydrochloric acid in alcohol might inhibit the splitting-off of the chlorine until the ring should be completely hydrogenated. This was found not to be the case, however, After absorption of six atoms of hydrogen per molecule, piperidine and pyridine were found in the solution, showing that the first stage in the hydrogenation of chlorpyridine is the formation of hydrochloric acid and pyridine.

4. The last compound tried as an intermediate in the synthesis was 2-methoxypyridine. The two steps required are obviously hydrogenation and methylation. Von Pechmann and Baltzer[12] first prepared 2-methoxypyridine by the action of methyl iodide on the silver salt of 2-pyridone, and later, von Pechmann[13] made it from 2-pyridone and diazomethane. Although 2-pyridone is now far more readily accessible[14] than it was at the time of von Pechmann's work, it is nevertheless

[11] Ber. 32 (1899), 1299.

[12] Von Pechmann and Baltzer, l.c.

[13] Von Pechmann, Ber. 28 (1895), 1624.

[14] Chichibabin and Rjasanzew, Centralb. 1916,II, 228.

more convenient to prepare 2-methoxypyridine as follows: 1-methyl 2-pyridone is converted by phosphorus pentachloride into 2-chlorpyridine[15] and this reacts with sodium methoxide in boiling methyl alcohol solution to give 2-methoxypyridine. Sell[16] studied the action of this reagent on 2,3,4,5, tetrachlorpyridine, but it has not previously been applied to 2-chlorpyridine. The hydrogenation of 2-methoxypyridine has not been studied, except with a view to proving its constitution; von Pechmann and Baltzer[17] found that the drastic action of sodium amalgam splits the ring, giving ammonia. It was tried by three methods:-

a. Sodium in boiling ethyl alcohol; method of Ladenburg[18]; also in boiling methyl alcohol, as it was anticipated that the lower temperature might make the reducing action less violent.

b. Electrolytic reduction, using lead electrodes[19].

c. Catalytically, using hydrogen at 3-2/3 atmospheres' pressure.

(1). In 40% acetic acid solution, with colloidal platinum.

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15. . Fischer, Ber. 32 (1899), 1298.
Fargher and Furness, J. Chem. Soc. 107 ('15),690.

16. Sell, J. Chem. Soc. 101 (1912), 1945.

17. Von Pechmann and Baltzer, l.c.

18. Ann. 247 (1888), 51.

19. Tafel, Ber. 33 (1900), 2209.

These methods proved too energetic; in each case, the methoxyl group was split off, yielding methyl alcohol and piperidine.

(2). In aqueous and in absolute methyl alcoholic hydrochloric acid, with platinum black, the amount of hydrogen absorbed being regulated.

The results show that the ring is hydrogenated before any methoxyl is split off, but the resulting methoxypiperidine is approximately as susceptible to hydrogenation as the pyridine ring. It appears that only minimal quantities of methoxypiperidine remain in the solution, and none has as yet been isolated,but the hydrogenation in absolute methyl alcohol is still being studied.

(3). In 95% methyl alcoholic hydrochloric acid, with platinum oxide, the hydrogenation being pushed to the limit. This experiment was done to find out if the platinum oxide would show an activity greater than that of platinum black, as was observed in the case of aminopyridine.
Not only did the methyl alcohol exhibit no restraining influence on the splitting-off of the methoxyl group, but the catalyst proved to be so active that the ring was broken; twelve atoms of hydrogen per molecule were absorbed, with formation of ammonia, and doubtless, normal pentane.

DISCUSSION OF RESULTS.

Taken as a whole, the results outlined above show the marked influence of the nitrogen atom on the carbon atoms adjacent to it in the pyridine ring, a fact which has been brought out by many authors.[20]

A consideration of the results of the hydrogenation of 1-methyl 2-pyridone and of 2-aminopyridine leads to the conclusion that these compounds behave as true dihydropyridine derivatives, and that there is no reason for considering further the anhydride formula proposed by O. Fischer for 1-methyl 2-pyridone,[21]. Gutbier[22], and Michaelis and Hölken[23], have adduced arguments in favor of this formula; on the other hand, Decker and Engler[24] showed convincingly that 1-methyl 2-quinolone must have the keto- structure, and, by analogy, the 1-methyl 2-pyridone must also. The best evidence hitherto advanced, however, in favor of the keto- form (I, above), is based on physical measurements. Baker and Baly[25], from a study of the absorption spectra of dilute solutions of the pyridones, declared in favor of the keto- form for the 2- and 4- isomers. The behavior of methyl

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[20] E.g., Mills and Smith, J. Chem. Soc. 121 (1922), 2724.

[21] O. Fischer, Ber. 31 (1898), 610.
O. Fischer and Demeler, Ber. 32 (1899), 1307.

[22] Gutbier, Ber. 33 (1900), 3358.

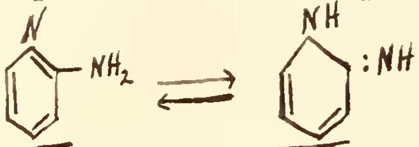
[23] Michaelis and Hölken, Ann. 331 (1904), 245.

[24] Decker and Engler, Ber. 36 (1903), 1171.

[25] Baker and Baly, J. Chem. Soc. 91 (1907), 1122.

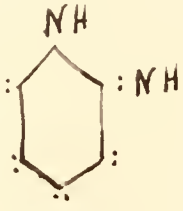
pyridone on hydrogenation now affords fairly conclusive proof of its structure. If it possessed the anhydride structure, it should take up six atoms of hydrogen, but it actually takes up only four, as would be expected of a dihydropyridine derivative. It thus behaves in accordance with the constitution expressed by the name; 1-methyl 2-keto-dihydropyridine(1,2).

Chichibabin[26] proved that aminopyridine exhibits tautomerism,



IV. VII.

just as von Pechmann and Baltzer proved in the case of 2-pyridone. He further showed that the imino- tautomer (VII) is the predominating one; and that this is to be considered a true dihydropyridine derivative, is proved by the fact that only four atoms of hydrogen are absorbed catalytically. Tautomer IV does, of course, exist, for it is the only form which could react with nitrous acid, Chichibabin having shown that the N-methyl derivative of VII is indifferent to this reagent. In an acid solution of the hydrogenated derivative, however, it must be concluded that there is no tautomerism, since the compound does not react with nitrous acid; its properties are evidently best expressed by the structure:-



VIII.

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26. Ber. 54 (1921), 814.

which represents it as a derivative not of tetrahydro- but of hexahydro-pyridine; viz., 2-iminopiperidine. In the free state, however, this base must exist to a slight extent in the tautomeric amino- form, for this is the only form which could give the Rimini reaction. Further evidence in support of structure VIII is found in the hydrolysis to 2-piperidone, just as the "N-methyl α-pyridone imide"* of Chichibabin was hydrolyzed to 1-methyl 2-pyridone. It is noteworthy that in order to undergo hydrolysis aminopyridine has to be "locked" in the form VII by a methyl group on the ring nitrogen, while its hydro- derivative (VIII) does not. On the other hand, it is to be anticipated that if locked in the amino- form (IV), as it is in dimethyl aminopyridine, it would take up six atoms of hydrogen, just as 2-pyridone locked in the hydroxy- form, as it is in methoxypyridine, takes up six.

The result of the hydrogenation of chlorpyridine is in agreement with the well-known high reactivity of the chlorine in the 2- position, contrasted to that in the 3- position. The ease with which methoxypiperidine is split, however, is surprising, in view of the great stability of methoxypyridine. The reason for this anomalous behavior must be that all 2- substituted piperidines with the side-chain linked through oxygen tend to revert to the stable piperidone structure; another demonstration of the influence of the nitrogen atom in the ring.

In regard to the activity of platinum oxide in the hydrogenation of amino- and of methoxypyridine, it is to be concluded that the oxide obtained by fusion of chlorplatinic acid with sodium nitrate is different from that which is formed

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*Better designated:- "1-methyl 2-imino-dihydropyridine (1,2)".

by the "regeneration" of exhausted platinum black by shaking with air. It is to be noted that only small amounts of the pyridine derivatives were used in the experiments with the oxide, and it is probable that the hydrogenation went farther than it did with platinum black simply because the oxide had not yet been completely reduced. The hydrogenations of the pyridine compound, and of the platinum oxide proceed simultaneously, and as soon as the oxide has been completely reduced, the extraordinary activity ceases. This would account for the difference in the degree of hydrogenation observed in the two cases; ring-splitting took place with methoxypyridine, whereas only one molecule of ammonia was split out of aminopyridine, the ring remaining intact. If equal amounts of platinum oxide were used, and equivalent amounts of the two pyridine derivatives, the extent of the hydrogenation would no doubt be the same in each case.

EXPERIMENTAL.

Pyridine was used as the starting point in these experiments; a commercial product labelled "H_2O....none; B.P. ...114" distilled from 98° to 119°. It was dried over phosphoric oxide for several days, and distilled; one liter then yielded 650 cc. of the fraction 114° - 116°, which was taken for synthesis.

Preparation of 1-methyl 2-pyridone.

Pyridine was converted, in 100 g. portions, into methyl pyridinium sulphate according to the directions of Decker and Kaufmann[27]. This product was transformed into 1-methyl 2-pyridone by the electrolytic oxidation method of O. Fischer and Neundlinger[28] improved by Fischer and Chur[29]. Owing to the miscibility of the pyridone with water, a maximum yield of 70% of the theoretical was obtained. About 2 kg. were prepared.

Apparatus for catalytic hydrogenation, and the preparation of platinum black.

The apparatus used for the catalytic hydrogenations described below has no advantage over that of Lochte, Noyes, and Bailey[30] except, possibly, that of simplicity. A "siphon bottle" of heavy glass, (obtained from a dealer in soda-fountain supplies), having a capacity of 800 cc., held the solution; it was joined to a cylinder of hydrogen by glass and rubber connections only.

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27. J. Prakt. Chem. (2), 84 (1911), 436.
28. Ber. 46 (1913), 2544.
29. J. Prakt. Chem. (2), 63 (1916), 363.
30. J. Am. Chem. Soc. 43 (1921), 2601.

The rubber tubing was reinforced by a layer of fabric, and showed no tendency to expand at four atmospheres' pressure. A reducing-valve on the hydrogen cylinder prevented a pressure greater than 3-2/3 atmospheres on the system. The glass tube leading from the siphon bottle passed through a cork, and was so bent as to prevent liquid from splashing up into the rubber tubing. By pouring a hot mixture of paraffin and beeswax over the cork, and clamping it in place with a perforated brass cap screwed over the "white-metal" threads on the siphon bottle, a gas-tight seal was effected. Between the bottle and tank two T-tubes were interposed, one leading to a manometer, and the other to a vacuum-pump. The manometer was empirically calibrated in intervals corresponding to 100 cc. measured at 22°, and 760 mm., 250 cc. of solution being in the siphon bottle. The calibration was checked by hydrogenating 1.089 g. of pyridine, in the presence of platinum black, that being the quantity required to absorb exactly one liter of hydrogen, measured at 22°, and 760 mm.

The platinum black was prepared by shaking platinum oxide,[31] suspended in dilute hydrochloric acid containing 1 g. of pyridine, with hydrogen under pressure. When no further absorption took place, the shaking bottle was disconnected, and the platinum filtered off. It was kept ready for use on the moist filter. Whenever, in the course of a hydrogenation with this catalyst, a marked diminution in the speed of absorption was observed, it was revivified by shaking with air at atmospheric pressure;

[31] Adams and Voorhees, l.c.

after five minutes, the manometer always indicated an absorption of 30 - 60 cc., and this quantity was not increased by prolonging the shaking to half an hour.

1. Catalytic hydrogenation of 1-methyl 2-pyridone.

Methyl pyridone, 23.3 g., was dissolved in 250 cc. of solution containing a slight excess of hydrochloric acid, and the platinum black, 0.5 g., washed from the filter into the bottle with this solution. After evacuating the system, and filling with hydrogen at a pressure of 3-2/3 atmospheres, the shaker was started. Thirty-five cc. per minute were absorbed, this rate not diminishing appreciably when the pressure fell to 1-1/2 atmospheres. When absorption ceased, the catalyst was shaken with air, but this was of no avail in this case, for on renewed shaking with hydrogen, there was no further absorption. Total volume absorbed.................. 10.37 l.

Calculated for 4 atoms per molecule, 22°, 10.34 l.

Evidently 1-methyl 2-piperidone was formed, instead of the desired 1-methyl 2-piperidol. After filtering from platinum, the solution was evaporated under diminished pressure, and the water and excess hydrogen chloride removed by four changes of absolute alcohol. No crystals appeared on cooling, even on addition of ether, so the syrup was put into a vacuum desiccator. After standing 24 hours, it solidified to a sticky mass of crystals; this was pressed between folds of filter paper, and recrystallized from water. The second and third crystallizations melted .

The base was prepared by shaking a 5% solution of the hydrochloride with a slight excess of silver oxide, the last traces of silver being removed as sulphide. The filtrate was

evaporated to 25 cc. and fractionated. 1-methyl 2-piperidone, boiling , was obtained.

Analysis gave C, %; H, %.

$C_6H_{11}O N$ requires C, %; H, %.

2. Preparation and hydrogenation of 2-aminopyridine.

Aminopyridine was prepared by the method of Chichibabin and Zeide[32], and purified by two vacuum distillations; boiling-point, 81° - 82° at 4 mm. The product thus obtained had a very slight yellow tinge, and melted sharply at 57°.

a. Hydrogenation in dilute HCl, with colloidal platinum as catalyst.

An "inoculation solution" was prepared by adding to 10 cc. of hot water 4 drops of each of the following solutions: 10% $H_2PtCl_6.6H_2O$, 10% gum acacia, 40% NaOH, 40% formaldehyde. When this mixture had become jet black, it was added to a solution of 1.5 g. of chlorplatinic acid, and 0.15 g. gum acacia in 100 cc. water. After addition of a distinct excess of hydrochloric acid, the mixture was shaken with hydrogen until reduction of the chlorplatinic acid was complete. Nine g. of aminopyridine with three equivalents of hydrochloric acid were then added, and the volume made up to 250 cc. The initial rate of absorption of hydrogen was 10 cc. per minute; after six hours, it fell to about 3 cc., so the catalyst was shaken with air. Absorption then took place at the initial rate, and stopped after two more hours. The treatment with air was repeated, but no more hydrogen

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[32] J. Russ. Phys.-Chem. Soc. 46, (1914), 1224.

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could be introduced, although shaking at 3-2/3 atmospheres was continued for half an hour. Total absorbed........... 4.60 l.
Calculated for 4 atoms per molecule, at 22°.............. 4.58 l.
The solution was evaporated to about 50 cc., and an equal volume of concentrated hydrochloric acid added, on boiling again, the platinum was completely precipitated and was filtered off. Evaporation was completed under diminished pressure.
The anhydrous hydrochloride was recrystallized from absolute alcohol; the second and third crystallizations melted 156°-7°.
Two samples were analyzed by the Kjeldahl-Gunning-Arnold method.
(1). N, 20.37%. (2). N, 20.86%.
$C_5H_{10}N_2.HCl$ requires N, 20.82%.

b. Hydrogenation in dilute HCl, with platinum black as catalyst.

A solution of 40.3 g. of 2-aminopyridine and 2 equivalents of hydrochloric acid in 250 cc., with 1.0 g. of platinum in suspension, was shaken with hydrogen at 3-2/3 atmospheres. Absorption took place at the rate of 50 cc. per minute, and ceased sharply when 20.4 l. had been taken up. Calculated for 4 atoms per molecule, 20.6 l. The salt was purified as above described, and used for the preparation of a few derivatives.
The chlorplatinate was prepared from 0.25 g. of the hydrochloride and 0.42 g. of chlorplatinic acid, and recrystallized from 60% alcohol; needles, with the characteristic orange color.
The salt was dried at 70°, and analyzed. Melting-point, 186.5°-7.5°, with decomposition. Found, (1) 32.26% Pt. (2) 32.19%.
$(C_5H_{10}N_2.HCl)_2PtCl_4$ requires.... 32.10% Pt.

The picrate was found to be almost insoluble in both cold and hot absolute alcohol. It is most conveniently crystallized from hot 40-60% alcohol, and may be washed with cold 95% alcohol without loss. After two crystallizations, it melted 207°-8°.

The benzoyl derivative was made from benzoyl chloride and excess sodium bicarbonate, and crystallized from alcohol. The third and fourth crystallizations melted 144.5°-5.0°.

Analysis gave C, %; H, %.

C H N O requires C, %; H, %.

The presence of the tautomeric 2-amino-tetrahydropyridine when the base is in the free state was indicated by a positive Rimini reaction (Mulliken, l.c.). A solution of 1 g. of the hydrochloride in 50 cc. of water was shaken for 30 minutes with a slight excess of thoroughly washed silver oxide, and filtered. To 5 cc. of this solution were added 1 cc. of pure acetone and 1 drop of 1% sodium nitroprusside. A clear violet-red color was developed within ten seconds after mixing. This color was given neither by piperidine nor by ammonia.

The action of nitrous acid in the cold was tried, using the proportions of reagents recommended by Knorr for piperidine[33], but the only substance isolated from the reaction mixture was unchanged 2-iminopiperidine hydrochloride, melting 156°-7°. The same result was obtained when the sodium nitrite was added to the acid solution at the boiling-point.

[33] L. Knorr, Ann. 221 (1883), 298.

Hydrolysis of 2-iminopiperidine.

On attempting to prepare the free base by decomposing a concentrated aqueous solution of the hydrochloride with potassium hydroxide, hydrolysis took place, with formation of ammonia and 2-piperidone. To ascertain the order of stability of the base, 10 g. of the hydrochloride were dissolved in 150 cc. of water, an excess of silver oxide added, and a current of nitrogen bubbled through the solution for 12 hours. The issuing gas was passed through hydrochloric acid solution, which was evaporated at the end of the run, but an insignificant residue, weighing less than 5 mg., was obtained.

The silver chloride was filtered off, and the experiment repeated with the solution of the free base at the boiling temperature. After 3 hours, the hydrochloric acid solution gave a residue of 3.55 g. on evaporation, which was shown to consist of ammonium chloride by analysis of its chlorplatinate. Found, 44.11% Pt. Calculated for $(NH_4Cl)_2PtCl_4$, 43.96% Pt. The other product of hydrolysis was identified as 2-piperidone.[34]

c. Hydrogenation in neutral aqueous solution, with platinum oxide as catalyst.

A solution of 3 g. of aminopyridine in 250 cc. water, with 1.164 g. of platinum oxide in suspension, was shaken with hydrogen until no more could be absorbed. The initial rate was 32 cc. per minute; the final rate, 8 cc. per minute.

Total volume absorbed....................................3.20 l.
Total volume calculated, (8 atoms per mol. & 169 cc. for PtO_2);3.24 l.

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[34] Schotten, Ber. 21 (1888), 2241.

During filtration, the odor of ammonia was quite distinct, which was to be expected, since piperidine is a stronger base than ammonia, and only one equivalent of hydrogen chloride was present. A slight excess of hydrochloric acid was added to the filtrate, and a portion of it treated with chlorplatinic acid. Ammonium chlorplatinate was precipitated; found, Pt 43.72%; calculated for $(NH_4)_2.PtCl_6$, Pt 43.96%.
The remainder of the filtrate was evaporated, and the alcohol soluble portion recrystallized, from alcohol and ether.
The third and fourth crystallizations melted 242°-3°, and this melting-point was not lowered by mixing with a sample of pure piperidine hydrochloride.

Attempt to hydrogenate 2-iminopiperidine with platinum black.

A neutral aqueous solution of 5 g. of 2-iminopiperidine hydrochloride, with 1 g. of platinum black in suspension, was shaken with hydrogen for one hour, but no absorption took place. After shaking with air, ~~the~~ the shaking with hydrogen was repeated, but the result was negative. The experiment was then tried in methyl alcoholic solution, but to no avail.

Attempt to hydrogenate 2-iminopiperidine to 2-aminopiperidine using platinum oxide as catalyst.

A neutral aqueous solution of 7.85 g. of 2-iminopiperidine hydrochloride with 1.164 g. of platinum oxide in suspension, was shaken with hydrogen until 1.2 l. had been absorbed. Required for 2 atoms per mol., at 22° and 760 mm., leaving out of account that used in the partial reduction of the platinum oxide, 1.4 l. The odor of ammonia was again observed during

filtration. The residue from evaporation of the filtrate was recrystallized five times from alcohol, but unsatisfactory melting-points were obtained. Separation was therefore tried by converting the bases into their picrates. The first four crops from the hot aqueous solution proved to consist of 2-iminopiperidine picrate, melting 207°; the fifth crop, obtained from the concentrated mother liquor by cooling to 0°, melted 145°-150°, and after two recrystallizations, at 151°-2°. This point was not changed by mixing with pure piperidine picrate. If 2-aminopiperidine had been formed in this experiment, no ammonia or piperidine should have been obtained, and only 15% of the 2-iminopiperidine should have been unchanged.

3. PREPARATION AND HYDROGENATION OF 2-CHLORPYRIDINE.

Chlorpyridine was prepared by Fargher and Furness' improvement of the method of O. Fischer (l.c.). It was found to be so slightly soluble in water that in the steam distillation of 180 g. portions, it was separated off and dried over potassium hydroxide, the water layer being discarded. Two distillations through a 40 cm. column sufficed to free it from the dichlorpyridine simultaneously formed; pure monochlorpyridine, boiling 171°-1.5°, was obtained. It has a quinoline-like odor, but being more volatile than quinoline, the odor is more pungent.

It was hydrogenated as follows: dry hydrogen chloride was passed into absolute alcohol at 0° until the increase in weight was 40 g. per 100 g. of alcohol, and 6 g. of chlorpyridine dissolved in 250 cc. of solution. This was shaken

with hydrogen at 3-2/3 atmospheres until 3.84 l., the volume required for 6 atoms per molecule, had been taken up. Rate of absorption, 13 cc. per minute. The residue obtained by evaporation of the solution was crystallized four times from alcohol; the third and fourth crystallizations melted 243°-4°, and this point was unchanged by admixture of the salt with pure piperidine hydrochloride. The mother-liquor from the first crop was alkalized, whereupon a powerful and unmistakable odor of pyridine, almost free from that of piperidine, was at once apparent.

4. PREPARATION AND HYDROGENATION OF 2-METHOXYPYRIDINE.

In the first trial, four equivalents of sodium methoxide to one of chlorpyridine were used, and this excess was later found to be necessary for a complete reaction.

A concentrated solution of sodium methoxide was prepared by dissolving 8 g. of sodium in 72 cc. of absolute methyl alcohol, and after cooling, 10 g. of chlorpyridine were added. The chlorpyridine dissolved on shaking, but did not begin to react until the solution was boiled. Refluxing was continued for six hours; the NaCl was then filtered off, washed with cold alcohol, dried, and weighed. Five g. were obtained, the theoretical quantity being 5.15 g. Excess hydrochloric acid was added to the reaction mixture, and most of the alcohol distilled through a long column. The base was set free by sodium hydroxide, and steam-distilled. It came over with twice its volume of water, but appeared to be more soluble than chlorpyridine, so the water layer was extracted with ether. The ether solution was dried with potassium carbonate,and

fractionated, using a 40 cm. column, as the last traces are held very tenaciously by the pyridine ether. The base distilled 142°-3°. Pure methoxypyridine, b.p , D has a pungent, unpleasant odor, but is not nauseating like pyridine. Analysis (Zeisel), gave % OCH_3.
C_6H_7ON requires %.

a. Reduction with sodium in ethyl alcohol.

Alcohol, 40 cc., and methoxypyridine, 5 g., were put into a 500 cc. balloon flask, and 15 g. of sodium, cut in small pieces and kept under ether, added through the condenser. When the violent boiling had subsided, the flask was immersed in an oil bath at 100°, and small portions of alcohol added at frequent intervals, to maintain rapid refluxing. When all the sodium had gone in solution, water was added, and steam passed in until the distillate showed no alkalinity. Hydrochloric acid was added in slight excess, and the solution evaporated to dryness. The crude product weighed 5 g. The third and fourth crystallizations from alcohol melted 242°-3°, and no lowering was produced by mixture with piperidine hydrochloride.
Analysis of the chlorplatinate gave (1). 33.59% Pt; (2). 33.47% Pt.
$(C_5H_{11}N.HCl)_2.PtCl_4$ requires 33.645% Pt.
A sample of 0.5 g. was boiled for one hour in the Zeisel apparatus, but the evolved vapors caused no precipitate in the alcoholic silver nitrate solution.

Reduction of 10 g. of methoxypyridine in absolute methyl alcohol, with 25 g. of sodium, also led to the splitting-off of the methoxyl group.

b. Electrolytic reduction in sulphuric acid solution, with lead electrodes.

The cathode was prepared according to the excellent and detailed directions of Tafel[19]. The area exposed to the solution was 36 sq. cm. Current densities of 10-14 amps/sq.dcm. were found to give satisfactory hydrogenation of pyridine, so the C.D. was kept within these limits in the experiments with methoxypyridine.

A solution of 5.g. of methoxypyridine in 110 cc. of 20% sulphuric acid was put into a porous clay cup, which was in a beaker of 20% sulphuric acid, and surrounded by a cooling coil, and the anode of sheet lead. The cathode was suspended in the center of the cell, by a closely-fitting rubber stopper; a glass tube passed through another hole in the stopper, and served as a means for collecting the escaping hydrogen. Coulombs required, 26,800. With the current regulated at 4.4 amperes, the time required for complete hydrogenation, if 100% of the hydrogen went into the ring, would be 1 hr. 58 min.The efficiency was less than 50%, however, for the hydrogen escaped from the cathode compartment at the rate of 17 cc. per minute at the start, and increased suddenly to 32 cc. after four hours had elapsed. The current was allowed to flow 15 minutes longer, the solution removed from the cell, alkalized, and steam-distilled. The distillate was acidified with hydrochloric acid, evaporated, and the salt crystallized from alcohol. The third crystallization melted 142°-3°. A 0.3 g. sample was boiled with hydriodic acid in the Zeisel apparatus for an hour, but no precipitate was formed in the alcoholic

silver nitrate solution.

c. Catalytic reduction in 40% acetic acid solution, using colloidal platinum.

The catalyst was prepared as described under 2-aminopyridine. The solution as finally made up contained 0.6 g. chlorplatinic acid, 0.3 g. gum acacia, 5 g. methoxypyridine, 50 cc. glacial acetic acid, and 70 cc. water. This was shaken with hydrogen until no more was absorbed; rate, slightly less than 1 cc. per minute. Piperidine hydrochloride was again identified as the reduction product.

d. Catalytic reduction, in aqueous hydrochloric acid, using platinum black.

In this and the succeeding hydrogenations of methoxypyridine, the volume of hydrogen was regulated. Required for 1 g. of methoxypyridine (6 atoms per mol.), measured at 22° and 760 mm., 665.5 cc; 1.503 g. require 1000 cc.

A solution of 2.67 g. of methoxypyridine in 250 cc. of solution containing a slight excess of hydrochloric acid, and 1.5 g. Pt was shaken with hydrogen until 1.78 l. had been absorbed. Rate, 75 cc. per minute. The resulting hydrochloride, after two crystallizations from alcohol, melted 241°-2.5°. This indicated that the methoxyl group is very easily split off by hydrogen; in order to identify all the products definitely, an experiment was done on a larger scale.

Proof that the first stage in the hydrogenation of methoxypyridine is the hydrogenation of the ring.

A solution containing 25 g. methoxypyridine and a slight excess of hydrochloric acid in 250 cc. was shaken with hydrogen

until 13 l., the quantity required to reduce just 20 g. to methoxypiperidine, had been absorbed. During filtration, the odor of methoxypyridine was apparent; the filtrate was made just alkaline to methyl orange, and the unchanged methoxypyridine distilled off with steam. The secondary base was freed by a slight excess of sodium hydroxide, and steam passed into the flask until the distillate had a neutral reaction. The acidified distillate left a residue of only 10.5 g.; after two crystallizations, it melted 242.5°-4.0°. Mixed with piperidine hydrochloride, it melted
The chlorplatinate melted 198°-9°, with decomposition. Analysis gave 33.48% Pt. Piperidine chlorplatinate requires 33.65%.

The alkaline solution in the distilling flask was neutralized with hydrochloric acid, evaporated, and the dried residue extracted with absolute alcohol. On distilling off the alcohol, a syrupy mass was obtained which would not solidify in a vacuum desiccator. It was transformed into a well-crystallized picrate, melting 173°-4° after four crystallizations. This purified fraction was, however, too small for analysis, and inasmuch as this experiment showed that the chief product consisted of piperidine, attention was turned to the hydrogenation in absolute methyl alcohol solution.

Hydrogenation in methyl alcoholic hydrochloric acid.

Dry hydrogen chloride was passed into 200 cc. of absolute methyl alcohol until the increase in weight was 12 g. Methoxypyridine, 14.9 g., was then added, and the volume made up to 250 cc. with methyl alcohol. The same platinum was used as in the previous experiment; it was washed twice with methyl

alcohol before being introduced into the siphon bottle. Absorption of hydrogen proceeded at the rate of 13 cc. per minute at first, but decreased gradually, due, probably, to the reduction of the oxide of platinum by the methyl alcohol. Hydrogenation was continued until 9.92 l., the volume required for 6 atoms per molecule, had been taken up; rate for the last liter, 8 cc. per minute. The third crystallization of the resulting hydrochloride melted 241.5°-3°. When mixed with pure piperidine hydrochloride, the m.p. was 242°-3°. No pure compound has as yet been isolated from the mother liquor.

Evidence that platinum oxide is more active in the hydrogenation of methoxypyridine than platinum black.

A solution containing 245 cc. 95% methyl alcohol, 5 cc. conc. hydrochloric acid, and 1.503 g. of methoxypyridine, was shaken with hydrogen in the presence of slightly more than 2 g. of platinum oxide. Initial rate of absorption, 180 cc. per minute. After absorption of 1.5 l., the volume corresponding, apparently, to the absorption of 8 atoms per molecule (1.33 l.), and the reduction of a portion of the platinum oxide, the rate fell to 30 cc. per minute. Absorption ceased entirely after a total of 2.2 l. had been taken up; this volume corresponds to 12 atoms per molecule (2.00 l.), the amount required to reduce methoxypyridine to ammonia and normal pentane, plus 0.2 l. for the reduction of the platinum oxide. The white salt obtained on evaporation of the solution was converted into the chlorplatinate. Analysis gave, Pt, 43.88%. $(NH4)_2PtCl_6$ requires Pt, 43.96%.

BIOGRAPHY.

The author of this dissertation was born in Richmond, Indiana, August 29, 1898. He received his preparatory education at the Friends School, Baltimore, where he graduated in 1915. During the years 1915-'18, he was a student at Oberlin College. From October, 1918, to January, 1919, he was a private in the Chemical Warfare Service of the U.S.Army, and was stationed at the Johns Hopkins Chemical Laboratory. In January, 1919, he was enrolled as a student in this University, and received the degree of A.B. the following June. Since October, 1919, he has been a graduate student in this University, with Chemistry for the principal subject, and Physical Chemistry and Pharmacology as subordinate subjects. He was awarded a University Scholarship for the 1919-'20, and Hopkins Scholarships in 1920-'21, and 1921-'22. He was appointed Du Pont de Nemours Fellow for the year 1922-'23.